Optimization of pediatric haematopoietic stem cell transplant outcomes through the application of pharmacokinetics and supportive care

Dupuis, L.L.E.

Citation for published version (APA):
This guideline provides clinicians caring for children with an approach to assessing the acute emetogenic potential of antineoplastic therapies. It was developed by an international, interprofessional panel of clinicians and researchers using AGREE and CAN-ADAPTE methods. The emetogenicity of antineoplastic agents was evaluated and ranked as high, moderate, low, or minimal. The emetogenicity of multiple-agent and multiple-day antineoplastic therapy was also classified. Gaps in the evidence used to underpin the guideline recommendations were identified. The contribution of this guideline to the prevention of antineoplastic-induced nausea and vomiting in individual children about to receive antineoplastic therapy requires prospective evaluation. Pediatr Blood Cancer 2011;57:191–198. © 2011 Wiley-Liss, Inc.

**Key words:** antineoplastics; antineoplastic-induced nausea and vomiting; chemotherapy-induced nausea and vomiting; emetogenicity; nausea; vomiting

**INTRODUCTION**

Antineoplastic-induced nausea and vomiting (AINV) reduces quality of life for all patients receiving antineoplastic therapy, including children. Nausea is identified by parents of children receiving active antineoplastic therapy in Ontario as the fourth most prevalent and bothersome treatment-related symptom seen in their children [1]. Current approaches to the selection of appropriate and effective measures to prevent AINV are founded on an accurate description of the potential of antineoplastic therapies to cause nausea and vomiting. However, no evidence-based, pediatric guideline for the classification of the emetic potential of antineoplastic agents exists.

The purpose of this guideline is to provide health care providers caring for children aged 1 month to 18 years who are receiving antineoplastic medication with an approach for assessing the emetogenic potential of antineoplastic regimens. The scope of this guideline is limited to the assessment of antineoplastic therapy emetogenicity in the acute phase (within 24 hr of administration of an antineoplastic agent). Its scope does not include anticipatory, breakthrough or delayed phase AINV, or nausea and vomiting that is related to radiation therapy, disease, co-incident conditions or end-of-life care. In addition, this guideline is most applicable to children who are naïve to antineoplastic therapy and who are about to receive their first course of antineoplastic therapy.

This guideline represents the first of a series of guidelines to address the need for, and the selection of, antiemetic prophylaxis and intervention in children with cancer receiving antineoplastic therapy. The complete version of the guideline summarized here can be accessed at http://www.pogo.ca/_media/File/Satellite/POGO%20Emetogenicity%20Classification%20Guideline%20Final-rev-%20251011.pdf.

**METHODS**

**Guideline Development Group**

The Pediatric Oncology Group of Ontario (POGO), a collaboration of the five pediatric oncology programs in Ontario, Canada identified AINV as a key supportive care initiative in 2008. Members of the POGO AINV Guideline Development Panel were selected with a view to obtain inter-professional representation from several POGO institutions as well as content expertise. Experts who had published in the area of AINV in children or who had a current research interest in AINV or supportive care in cancer were invited to join the guideline development group.

**Source Guideline Selection**

A comprehensive literature review and environmental scan were conducted to identify existing guidelines for the classification of the emetogenicity of antineoplastic therapies for...
children and youth with cancer. Searches were conducted through March 2010 with the assistance of a library scientist. Details of the literature search and environmental scan are available at http://www.pogo.ca/_media/File/Satellite/POGO%20Emetogenicity%20Classification%20Guideline%20Final-rev-%20251011.pdf. Panel members also identified guidelines for the classification of the emetogenicity of antineoplastic agents for children and youth with cancer from their institutions as well as from other agencies and associations with which they had affiliations.

A source guideline was sought which addressed the health questions that framed the development of this guideline (Table I) and could be adapted to the POGO context. Each guideline identified through the search was independently reviewed and scored by four to six members of the panel using the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument [2].

**Pediatric Evidence Identification and Synthesis**

The guideline selected for adaptation, the source guideline, was to be updated by literature published since its development and, where necessary, with pediatric experience. Thus a literature search focused on the AINV experienced by children was conducted with the assistance of a librarian scientist. All types of published primary evidence were included in this search. Details of the search strategy employed are available at http://www.pogo.ca/_media/File/Satellite/POGO%20Emetogenicity%20Classification%20Guideline%20Final-rev-%20251011.pdf. Pediatric references and sources obtained through on-line database searches, references cited in the papers obtained through this search, papers gleaned from the personal files of panel members, and unpublished supplementary data from the research of panel members were evaluated for inclusion in the POGO guideline. Where the source guideline did not include an antineoplastic agent used in pediatric oncology and in the absence of other information, the emetogenicity ranking of one of the other guidelines previously identified and evaluated was employed (Table II). The quality of evidence and strength of recommendations were assessed [3,4] by the lead author and confirmed through discussion by the remaining panel members.

Outcomes of interest included: proportion of children receiving antineoplastic therapy that attained complete AINV control (defined as either no vomiting and no nausea or no vomiting) during the acute phase and proportion of children receiving antineoplastic therapy that experienced failed AINV control (defined as 3 or more emetic episodes in 24 hr) during the acute phase.

**TABLE I. Health Questions That Guided Development of the Guideline**

<table>
<thead>
<tr>
<th>Question</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Which antineoplastic agents carry a high, moderate, low, or minimal</td>
<td>60%</td>
</tr>
<tr>
<td>risk of acute phase AINV when given as single agents to children?</td>
<td></td>
</tr>
<tr>
<td>2. Is the emetogenic potential of multi-agent, single day antineoplastic</td>
<td>60%</td>
</tr>
<tr>
<td>therapy different from that of the most emetogenic antineoplastic agent</td>
<td></td>
</tr>
<tr>
<td>given?</td>
<td></td>
</tr>
<tr>
<td>3. Is the emetogenic potential of multiple day antineoplastic therapy</td>
<td>60%</td>
</tr>
<tr>
<td>regimens different from that of single day antineoplastic therapy?</td>
<td></td>
</tr>
<tr>
<td>4. Where are the gaps in the evidence supporting the classification of the</td>
<td>60%</td>
</tr>
<tr>
<td>emetogenic potential of antineoplastic therapy in children?</td>
<td></td>
</tr>
</tbody>
</table>

Expected rates of complete AINV control in children receiving antineoplastic agents of high, moderate, minimal, and low emetic risk who were not given antiemetic prophylaxis or who were given prophylaxis which we now know to be ineffective were: <10%, 10 to <30%, 30 to <90%, and >90%, respectively. The expected rate of complete AINV control in children receiving modern antiemetic prophylaxis (5-HT3 antagonist with/without dexamethasone) was greater than 70–80%. Reports of AINV by children who did not receive antiemetic prophylaxis or who received antiemetic prophylaxis which we now know to be inadequate was weighted more highly than experience of children given effective antiemetic prophylaxis.

In the event of contradictory information, panel members took a conservative approach; that is, the higher emetogenicity risk ranking was applied to an agent or combination of agents. This approach is less likely to lead to breakthrough AINV and would allow reduction of antiemetic prophylaxis, if desired, in a patient who was well-controlled. Decisions were taken through panel discussions and any differences in opinion were resolved by consensus. If consensus was unable to be reached on any matter, a decision was made by the majority of panel members by a vote.

**External Review and Consultation Process**

Physicians, nurses and pharmacists with an active clinical and/or research interest in AINV were asked to review the draft guideline using a questionnaire. The feedback of these 12 content experts was discussed in detail by the panel and a decision on each item was taken by consensus. When the decision of the panel was not unanimous, a revision was made if it was supported by at least 60% of the guideline development panel members. Physician, nurse and pharmacist members of POGO centers and their satellites and physician, nurse and pharmacist members of C17 (an association of the Canadian tertiary care pediatric Hematology/Oncology centers) were then asked to review the revised draft guideline using a questionnaire. The feedback from 29 health care providers from 14 different institutions was discussed in detail by the panel; revisions were made to the guideline as discussed above.

**RESULTS**

Six guidelines that were either developed for use in adults [5–8] or for use in children [9,10] using consensus-based or undisclosed methodologies were identified and assessed using the AGREE Instrument. Based on its robust AGREE scores (see http://www.pogo.ca/_media/File/Satellite/POGO%20Emetogenicity%20Classification%20Guideline%20Final-rev-%20251011.pdf), it was the unanimous decision to accept the National Comprehensive Cancer Network’s (NCCN) guideline “Antiemesis v.2 2008” [8] as the source guideline for adaptation. Advantages of the NCCN guideline included its timeliness, inclusion of newer agents, and delineation of emetogenicity based on antineoplastic dose for many agents. When the NCCN guideline was subsequently updated, the newer version [11] was compared to the previous version. Since the emetogenicity classification in the newer version did not differ from that presented in the 2008 version, v3.2009 was cited as the source guideline. Panel members agreed to include all agents which appear in the NCCN guideline in the POGO guideline regardless of their current...
### TABLE II. Classification of the Acute Emetogenic Potential of Antineoplastic Medication in Pediatric Cancer Patients Given Intravenously (Unless Stated Otherwise) as Single Agents

<table>
<thead>
<tr>
<th>Level of Emetic Risk</th>
<th>High level of emetic risk (&gt;90% frequency of emesis in absence of prophylaxis)</th>
<th>Moderate level of emetic risk (30–90% frequency of emesis in absence of prophylaxis)</th>
<th>Low level of emetic risk (10 to &lt;30% frequency of emesis in absence of prophylaxis)</th>
<th>Minimal (&lt;10% frequency of emesis in absence of prophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Altretamine</td>
<td>Aldesleukin &gt;12 to 15 million U/m²</td>
<td>Amifostine ≤300 mg/m²</td>
<td>Alemtuzumab</td>
</tr>
<tr>
<td></td>
<td>²Dactinomycin</td>
<td>Etoposide (oral)</td>
<td>Amascrine</td>
<td>Lenalidomide</td>
</tr>
<tr>
<td></td>
<td>Carboptatin</td>
<td>Idarubicin</td>
<td>Bexarotene</td>
<td>Alpha interferon</td>
</tr>
<tr>
<td></td>
<td>Carmustine &gt;250 mg/m²</td>
<td>Ifosfamide</td>
<td>Capecitabine</td>
<td>Asparaginase (IM or IV)</td>
</tr>
<tr>
<td></td>
<td>²Cisplatin</td>
<td>Melphalan &gt;50 mg/m²</td>
<td>Cytarabine ≤200 mg/m²</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td></td>
<td>²Cyclophosphamide ≥1 g/m²</td>
<td>Methotrexate ≥250 mg to &lt;12 g/m²</td>
<td>Paclitaxel</td>
<td>Bleomycin</td>
</tr>
<tr>
<td></td>
<td>²Cytarabine 3 g/m²/dose</td>
<td>Oxaliplatin &gt;75 mg/m²</td>
<td>Mitomycin</td>
<td>Bortezomib</td>
</tr>
<tr>
<td></td>
<td>Dacarbazine</td>
<td>Temozolomide (oral)</td>
<td>Nilotinib</td>
<td>Busulfan (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cetuximab</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chlorambucil (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cladribine (2-chlorodeoxyadenosine)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Decitabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Denileukin diftitox</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dexrazoxane</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Erlotinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fludarabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gefitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gemtuzumab ozogamicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hydroxyurea (oral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lapatinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All agents given intravenously (IV) unless stated otherwise. ²Pediatric evidence available.
relevance to pediatric oncology since these agents may be administered to individual children with rare diseases or enter the pediatric domain at a later date. Panel members also unanimously decided to adapt the Hesketh 1997 paper [6] to inform the classification of combination antineoplastic therapies commonly used in pediatrics.

The POGO emetogenicity classification guideline is summarized in Table III. The evidence supporting the guideline recommendations is presented below. More detail is available in the supplementary tables available online.

Which Antineoplastic Agents Carry a High Risk of Acute Phase AINV When Given as Single Agents to Children?

Available pediatric experience confirms the source guideline’s ranking of cisplatin ≥50 mg/m² and cyclophosphamide >1.5 g/m² as highly emetogenic antineoplastic agents when given as single agents. The rationale for changes from the source guideline [11] is summarized below.

Carboplatin. The determination of the risk of carboplatin-induced AINV was complicated by contradictory evidence. Three studies evaluated acute AINV in children receiving 30, 63 or in one case an unknown number of courses of carboplatin with antiemetic prophylaxis [12–14]. The AINV control reported in these studies placed carboplatin as either a high-risk [12,13] or a moderate-risk [14] emetogen. Given the very small numbers of patients evaluated, the use of non-validated or unknown nausea severity assessment instruments in the two studies supporting the classification of carboplatin as a moderate emetogen and the prevailing conservative philosophy of the panel, carboplatin was ranked as a highly emetogenic agent.

Cisplatin. The source guideline ranks cisplatin as a high-risk emetogen at doses of 50 mg/m² or more. This finding was confirmed by pediatric experience [13–17]. In addition, poor AINV control associated with cisplatin doses less than 50 mg/m² was reported in two studies that evaluated 11 and 7 courses [15,18]. One study incorporated an arm where no antiemetic prophylaxis was given. The poor AINV control observed by patients evaluated in both studies placed cisplatin as a high-risk emetogen when given in doses less than 50 mg/m².

Cyclophosphamide. Several pediatric studies have confirmed the high emetogenicity of cyclophosphamide in doses of 1.5 g/m² (50 mg/kg) or more [13,19,20]. Yet, a single study that evaluated 40 courses of cyclophosphamide 1 to less than 2 g/m² (33 to <67 mg/kg) reported a poor AINV control despite administration of antiemetic prophylaxis [13]. The proportion of patients or cycles receiving cyclophosphamide doses between 1 and 1.5 g/m² is unknown. In keeping with the conservative philosophy of the guideline development panel, the decision was made to rank cyclophosphamide in doses of ≥1 g/m² as highly emetogenic.

Cytarabine. The source guideline ranks cytarabine in doses 1 g/m² and greater as a moderate emetogen. Three pediatric studies observed poor AINV control following administration of cytarabine in doses of 3 g/m² or more [13,16,21]. One of these studies incorporated an arm where no antiemetic prophylaxis was given [21], another study provided antiemetic prophylaxis now known to be inadequate in one arm [16] while the third provided ondansetron for prophylaxis [13]. The poor level of AINV control observed in these studies places cytarabine 3 g/m² or more as a high-risk emetogen.

Dactinomycin. The source guideline ranks dactinomycin as a moderate emetogen. However, the single pediatric study identified that described dactinomycin-associated AINV observed complete control of both acute phase vomiting and nausea in four of five patients receiving dactinomycin 45 μg/kg with ondansetron plus dexamethasone as prophylaxis [13]. This level of response to ondansetron plus dexamethasone prophylaxis places dactinomycin as a high-risk emetogen.

Methotrexate ≥12 g/m². The source guideline ranks methotrexate 250 mg/m² or more as a moderate emetogen. However, a single study describes the AINV experience of seven children receiving 26 courses of methotrexate 12 g/m² [13]. With ondansetron plus dexamethasone given as AINV prophylaxis, 60% of patients achieved complete control of both vomiting and nausea. This level of response to ondansetron plus dexamethasone prophylaxis places methotrexate 12 g/m² as a high-risk emetogen.

Thiotepa. Thiotepa does not appear in the source guideline. Three studies were identified that provided information regarding the incidence of emesis following thiotepa administration to 2, 18, and 9 children, respectively [22–24]. All describe poor AINV control despite administration of ondansetron in two studies. Although the number of children whose emetic response to thiotepa has been evaluated is small, the poor response to ondansetron

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of supporting evidence [3,4]</th>
<th>Grade of recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>The single antineoplastic agents provided in Table II have high emetogenic potential in children</td>
<td>Low to very low</td>
<td>1C</td>
</tr>
<tr>
<td>The single antineoplastic agents provided in Table II have moderate emetogenic potential in children</td>
<td>Low to very low</td>
<td>1C</td>
</tr>
<tr>
<td>The single antineoplastic agents provided in Table II have low emetogenic potential in children</td>
<td>Low to very low</td>
<td>1C</td>
</tr>
<tr>
<td>With the exceptions noted in Table III, the emetogenicity of multiple agent, single day antineoplastic therapy given to children is classified based on the emetogenic potential of the most highly emetogenic agent in the combination to be given</td>
<td>Very low</td>
<td>1C</td>
</tr>
<tr>
<td>The emetogenicity of multiple day antineoplastic therapy is classified in children based on the emetogenic potential of the most highly emetogenic agent(s) on each day of therapy</td>
<td>Low to very low</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not available—recommendation of source guideline was adopted without revision.

*Pediatr Blood Cancer* DOI 10.1002/pbc
prophylaxis suggests that it presents a high emetic risk, at least in doses of 300 mg/m² or more.

**Which Antineoplastic Agents Carry a Moderate Risk of Acute Phase AINV When Given as Single Agents to Children?**

Available pediatric experience confirms the source guideline’s ranking of carmustine ≤250 mg/m² [25], cyclophosphamide ≤1 g/m² [25], daunorubicin [13], and doxorubicin [13,26] as moderately emetogenic antineoplastic agents when given as single agents. Changes from the source guideline [11] that stem from the first recommendation are: deletion of cisplatin <50 mg/m², carboplatin, and dactinomycin; and capping the cytarabine dose at 3 g/m². The rationale for other changes from the source guideline is summarized below.

**Busulfan IV.** The source guideline did not explicitly include information regarding IV busulfan [10]. Busulfan in doses >4 mg/day was ranked as a moderate emetic risk while busulfan (no dose provided) was ranked as a minimal emetic risk. In neither case was the route of administration described. Busulfan IV is typically given to children as part of HSCT conditioning in initial doses ranging from 3.2 to 4.8 mg/kg/day [27]. Thus the dose of 4 mg/day stipulated in the source guideline is not relevant to pediatric practice and was removed. The Busulfex™ product monograph describes a 43% incidence of vomiting during IV busulfan administration [28]. Information regarding the type of AINV prophylaxis provided in these studies is not provided. Based on this information, IV busulfan at any dose is ranked as a moderate emetogen.

**Clofarabine.** Of the guidelines identified in the search for a source guideline for adaptation, only the guideline of the Children’s Oncology Group included clofarabine and ranked it as a moderate emetogen with a frequency of emesis of 60–90%. Published experience regarding the incidence of clofarabine-induced AINV was not identified. The incidences of nausea and vomiting reported in the product monograph are 73% and 78% respectively though no time frame is given for this information, nor is it known whether observations were made in the absence or presence of AINV prophylaxis [29].

Nausea or vomiting were reported in 19 of 25 patients aged 1–19 years (76%) receiving clofarabine in a phase I trial [30]. Nausea of grade 3 or higher (i.e., leading to inadequate oral caloric/fluid intake requiring supplementation, life-threatening consequences, or death) was reported after 10 of 122 treatment cycles in a phase II trial [31]. Information regarding the administration of antiemetic prophylaxis is not provided in either report. Assuming that the frequency of acute phase AINV associated with clofarabine is 70–80% in the absence of AINV prophylaxis and in keeping with the conservative philosophy of the guideline development panel, clofarabine was ranked as a moderate-risk emetogen.

**Cytarabine.** The source guideline made no provision for cytarabine doses <100 mg/m². In keeping with the guideline development panel’s desire to eliminate such gaps and with its conservative philosophy, cytarabine >200 mg/m² was classified as a moderate-risk emetogen.

Intrathecal therapy: methotrexate, cytarabine, and hydrocortisone. The source guideline did not assess the emetogenicity of intrathecal therapy. Nausea and/or vomiting associated with triple agent (methotrexate, cytarabine, and hydrocortisone) intrathecal (ITT) administration has been assessed in children [32,33]. Complete control of both nausea and vomiting were observed in 13% [32] and 37% [33] of courses when antiemetic prophylaxis was not given. The poor control of AINV reported in these studies places ITT as a moderate-risk emetogen.

**Which Antineoplastic Agents Carry a Low Risk of Acute Phase AINV When Given as Single Agents to Children?**

No pediatric experience was identified that was applicable to the determination of agents of low emetic risk other than for oral busulfan. The rationale for changes from the source guideline [11] is summarized below.

**Amsacrine.** Amsacrine did not appear in the source guideline. Due to the lack of published pediatric experience regarding the emetogenicity of amsacrine, the other guidelines which were identified in the process of selecting the source guideline for adaptation were consulted [5–7,10]. Amsacrine was not listed in any of these documents. Cancer Care Ontario [34] and the British Columbia Cancer Agency [35] state the incidence of amsacrine-induced vomiting to be 10–30% and 10%, respectively. Based on this information, amsacrine was ranked as a low risk emetogen.

**Busulfan (oral).** The source guideline did not explicitly include information regarding oral busulfan [10]. Busulfan in doses >4 mg/day was ranked as a moderateemetogen while busulfan (no dose provided) was ranked as having minimal emetic risk. In neither case was the route of administration described. Supplementary data obtained from Kusnierczyk et al. [20] support the assignment of oral busulfan given as part of HSCT conditioning as being of low emetic risk. These children received ondansetron every 12 hr during the 4 days of oral busulfan administration. Children did not vomit during six of seven oral busulfan courses and were protected from vomiting on 25 of 28 days when oral busulfan was administered. Based on this information, oral busulfan was classified as a low-risk emetogen.

**Cytarabine.** The source guideline had no provision for cytarabine doses <100 mg/m². In keeping with the guideline development panel’s desire to eliminate such gaps and with its conservative philosophy, cytarabine <100 mg/m² was classified as a low-risk emetogen.

**Teniposide.** Teniposide was not included in the source guideline. A single pediatric study whose primary aim was to evaluate the effect of teniposide on magnesium homeostasis also reported the incidence of vomiting associated with both cisplatin (day 1) and teniposide (day 3) [17]. No vomiting was observed after teniposide administration. Both Cancer Care Ontario [34] and the Children’s Oncology Group Supportive Care Guidelines [10] classify teniposide as an emetogen of low potency. In the absence of specific evidence, teniposide was classified as being of low emetogenic potential in the POGO guideline.

**Thiotepa.** Thiotepa at any dose was not included in the source guideline. Thiotepa ≥300 mg/m² has been classified as a high-risk emetogen in this guideline (see the first recommendation). In alignment with the desire to avoid gaps in the dose range of agents included in this guideline, thiotepa in lower doses of was classified as a low-risk emetogen based on its classification in the COG Supportive Care Guidelines [10].

*Pediatr Blood Cancer* DOI 10.1002/pbc
Which Antineoplastic Agents Carry a Minimal Risk of Acute Phase AINV When Given as Single Agents to Children?

No pediatric experience was identified that informed the determination of agents of minimal emetic risk. The list of minimal emetogens in the source guideline included asparaginase but did not differentiate between the various asparaginase products available: native asparaginase, Erwinia asparaginase or Peg-asparaginase. No literature specific to the emetogenicity of Peg-asparaginase was located. The ranking of the source guideline was therefore accepted and interpreted to be applicable to all available asparaginase products.

No literature regarding AINV experienced by children receiving oral mercaptopurine and vindesine was identified. The Children’s Oncology Group Supportive Care Guidelines [10] classify both of these agents as emetogens of minimal potency. In the absence of specific evidence, this classification was adopted in the POGO guideline. Changes from the source guideline are: deletion of busulfan (see the first and second recommendations), and addition of mercaptopurine (oral) and vindesine (as per COG Supportive Care Guidelines [10]).

Is the Emetogenic Potential of Multi-Agent, Single Day Antineoplastic Therapy Different From That of the Most Emetogenic Antineoplastic Agent Given?

Pediatric experience confirms the recommendation of the source guideline to base the emetogenicity of a combination antineoplastic regimen on that of the agent of highest emetic risk for many combinations [13,16,21,36–38]. The emetogenicity of the antineoplastic combinations listed in Table IV appear to be more emetogenic than would be appreciated by assessment of the emetic risk of the individual agents [13,14,25,39]. In step with the conservative approach of the panel the emetogenicity of these combinations was ranked higher than their most emetogenic single agent constituent.

Hesketh et al. [6] developed a process for the evaluation of the emetogenicity of combination antineoplastic therapy in adults. With the exception of low-dose cytarabine which was not included in the Hesketh classification system, the antineoplastic combinations we have determined to be more emetogenic than their most emetogenic single constituent would also be ranked higher using the Hesketh system. A more detailed assessment of the antineoplastic combinations listed in Table IV using the Hesketh system was included in the version of this guideline that was sent to the expert reviewers. At their suggestion, incorporation of the Hesketh classification system was deleted from the final version of the POGO guideline. The Hesketh system of evaluating the emetogenicity of antineoplastic combinations is no longer included in guidelines for adult oncology patients.

Is the Emetogenic Potential of Multiple Day Antineoplastic Therapy Regimens Different From That of Single Day Antineoplastic Therapy?

No pediatric experience was identified that was applicable to the determination of the risk of AINV with multiple day antineoplastic therapy. The recommendation of the source guideline that the emetogenicity of multiple day antineoplastic therapy be classified based on the emetic risk of the most highly emetogenic agent on each day of therapy was adopted.

Where Are the Gaps in the Evidence Supporting the Classification of the Emetogenic Potential of Antineoplastic Therapy in Children?

Clearly there are many gaps in the evidence regarding the emetogenicity of antineoplastic agents in children. Specifically, no pediatric literature was located regarding the risk of AINV in children receiving aldesleukin, altretamine, amifostine, arsenic trioxide, azacitidine, bendamustine, IV busulfan, carmustine >250 mg/m², cyclophosphamide (oral), cytarabine 1 to <3 g/m², dacarbazine, idarubicin, ifosfamide, imatinib (oral), irinotecan, lomustine, mechlorethamine, melphalan >50 mg/m², methotrexate 250 to <12 g/m², oxaliplatin >75 mg/m², oral procarbazine, streptozocin, temozolomide (oral) or vinorelbine (oral). The lack of pediatric information which is available to inform the emetogenicity classification of agents deemed to be of low emetic risk in adults is glaring. The need for information specific to children is especially pressing for antineoplastic agents that are commonly used in pediatric treatment protocols such as asmsacrine, cytarabine <200 mg/m², methotrexate 50 to <250 mg/m², mitoxantrone, paclitaxel, etoposide, teniposide, thiotepa, and topotecan.

No information was identified that confirms or refutes the emetogenicity classification of agents deemed to be of minimal emetic risk in adults for application to pediatric practice. Once again, the need for information specific to children is especially pressing for antineoplastic agents that are often included in pediatric treatment protocols such as asparaginase, bleomycin, cladribine, fludarabine, gemtuzumab, hydroxyurea, mercaptopurine (oral), methotrexate ≤50 mg/m², Peg-asparaginase, rituximab, thioguanine (oral), vinblastine, vincristine, vindesine, and vinorelbine.

Since the existing pediatric evidence is derived from a very small number of patients and nausea severity assessment was often not included as a study endpoint or was assessed using an unvalidated instrument, additional pediatric evidence is required to improve confidence in all the emetogenicity rankings proposed. In particular, the risk of AINV following intrathecal administration of medications other than the combination of

---

TABLE IV. Classification of the Acute Emetogenic Potential of Specific Antineoplastic Medication in Pediatric Cancer Patients Given in Combination

<table>
<thead>
<tr>
<th>High level of emetic risk (&gt;90% frequency of emesis in absence of prophylaxis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide + anthracycline</td>
</tr>
<tr>
<td><em>Cyclophosphamide + doxorubicin</em></td>
</tr>
<tr>
<td><em>Cyclophosphamide + epirubicin</em></td>
</tr>
<tr>
<td><em>Cyclophosphamide + etoposide</em></td>
</tr>
<tr>
<td><em>Cytarabine 150–200 mg/m² + daunorubicin</em></td>
</tr>
<tr>
<td><em>Cytarabine 150–300 mg/m² + etoposide</em></td>
</tr>
<tr>
<td><em>Cytarabine 300 mg/m² + teniposide</em></td>
</tr>
<tr>
<td><em>Doxorubicin + ifosfamide</em></td>
</tr>
<tr>
<td>Doxorubicin + methotrexate 5 g/m²</td>
</tr>
<tr>
<td><em>Etoposide + ifosfamide</em></td>
</tr>
</tbody>
</table>

All agents given intravenously (IV) unless stated otherwise. *Pediatric evidence available.

Pediatr Blood Cancer DOI 10.1002/pbc
methotrexate, cytarabine and hydrocortisone, the emetogenicity of cytarabine in doses >200 mg/m² to <1 g/m² and of oral busulfan and the potential dose-dependent emetogenicity of IV etoposide all merit investigation. Furthermore, given that both combination and multiple day antineoplastic therapy are common in pediatric oncology practice, it is imperative that the emetogenicity of common single-day and multiple-day antineoplastic combinations be investigated.

Finally, the range of emetic potential encompassed in the category of moderately emetogenic (30–90% risk) adopted from the source guideline [11] is overly broad. More pediatric experience is required to more fully inform the risk of AINV with the agents categorized as moderate emetogens to distinguish those which are truly moderate emetogens (e.g., 30–60% risk) from those which carry a moderately high risk of AINV (e.g., 60–90% risk).

CONCLUSIONS

Knowledge of the inherent emetogenicity of antineoplastic therapies is a key step toward control of AINV. Evidence regarding the propensity of individual and combination antineoplastic agents to lead to nausea and/or vomiting in children is often lacking. As a result, the experience of adult cancer patients is used to inform the emetogenicity ranking and the selection of antiemetic prophylaxis in children. In practice, AINV control is often less than ideal [13,26,40–43]. The reasons for this are multifactorial; however, selection of antiemetic prophylaxis based on an inaccurate assessment or under appreciation of the emetic risks presented by antineoplastic agents may contribute to poor AINV control. This guideline is intended to assist pediatric clinicians to select effective antiemetic prophylaxis for children receiving anti-neoplastic therapy. Prior to its development, an evidence-based, pediatric emetogenicity guideline was not available. These guidelines will lead to improvements in the supportive care of children with cancer by offering a transparent, consistent, evidence-based approach to the assessment of emetic risk of treatment.

Users of this guideline are encouraged to incorporate its recommendations into systems in place in their institutions which facilitate the prescription of antineoplastic and antiemetic therapy such as: antineoplastic treatment protocols and road maps; institutional guidelines for selection of antiemetic agents for the prevention of acute AINV, and pre-printed or electronic (e.g., CPOE) order sets that include antineoplastic agents. In this way, a consistent approach to antiemetic selection can be applied and outcomes assessed. Prospective, rigorous evaluation of the prevalence and severity of AINV in children receiving specific antineoplastic therapies in conjunction with specific antiemetic interventions is needed to address the many existing research gaps.

ACKNOWLEDGMENT

The counsel of Ms. Carol Digout and Dr. Dorothy Barnard with respect to the AGREE and CAN-ADAPTE methodologies; the assistance of Ms. Elizabeth Uleryk, Director, Hospital Library, The Hospital for Sick Children with the literature and guideline searches, and the administrative assistance of Ms. Carla Bennett, Coordinator of Clinical Programs, Pediatric Oncology Group of Ontario are gratefully acknowledged. The submission of a review from the following content reviewers is also acknowledged: Ms. Christina Baggott, Ms. Rebecca Clark-Snow, Dr. Yifan Rannan Eliya, Dr. Steven Grunberg, Dr. Paul Hesketh, Ms. Karin Jordan, Dr. Anne Marie Langelin, Dr. Kathryn Mannix, Mr. Tom Oliver, Dr. Andrea Orsey, Dr. M.D. van der Wetering, and Ms. Deborah Woods. This study was supported by the Pediatric Oncology Group of Ontario; Ministry of Health and Long Term Care, Ontario; Children’s Oncology Group (L.S. and L.L.D.).

REFERENCES


Pediatr Blood Cancer DOI 10.1002/pbc
Dupuis et al.